CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214916Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 123140

MEETING MINUTES

Cara Therapeutics, Inc.
Attention: Edward Liao, PharmD
Head of Regulatory Affairs
4 Stamford Plaza, 9th Floor
Stamford, CT 06902

Dear Dr. Liao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for difelikefalin intravenous solution.

We also refer to the telecon between representatives of your firm and the FDA on May 13, 2020. The purpose of the meeting was to discuss the continued development program for difelikefalin as well as to facilitate the planning of the New Drug Application (NDA) submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Harmon, Regulatory Project Manager at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Kendall Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Agenda

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 13, 2020, 9:00 a.m. – 10:00 a.m. DST
Meeting Location:	Teleconference
Application Number:	IND 123140
Product Name:	difelikefalin intravenous solution
Proposed Indication:	For the treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adult patients undergoing hemodialysis (HD)
Sponsor Name:	Cara Therapeutics, Inc.
Regulatory Pathway:	505(b)(1) of the Food, Drug, and Cosmetics Act
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Jennifer Harmon, PharmD

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
David Kettl, MD, FAAP, Clinical Team Leader, DDD
Gary Chiang, MD, Clinical Reviewer, DDD
Matthew Guerra, PhD, Biometrics Reviewer, Division of Biometrics III
Katherine R. Bonson, Ph.D., Senior Pharmacologist, Controlled Substance Staff
Barbara Gould, MBAHCM, Chief, Project Management Staff,
Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)
Jennifer Harmon, PharmD, Regulatory Health Project Manager, DRO – DD

SPONSOR ATTENDEES

Frédérique Menzaghi, PhD, Chief Scientific Officer, Cara Therapeutics, Inc.
Joana Goncalves, MD, Chief Medical Officer, Cara Therapeutics, Inc.
Catherine Munera, PhD, Vice President, Head of Biometrics, Cara Therapeutics, Inc.
Warren Wen, PhD, Vice President, Clinical Research and Development, Cara Therapeutics, Inc.
Andrew Albright, Executive Director, Program Management, Cara Therapeutics, Inc.
Edward Liao, PharmD, Head of Regulatory Affairs, Cara Therapeutics, Inc.
Georgine Ragsdale, PharmD, Associate Director, Regulatory Affairs, Cara Therapeutics, Inc.

1.0 BACKGROUND

The purpose of this meeting is to discuss the continued development program for difelikefalin intravenous solution as well as to facilitate the planning of the New Drug Application (NDA) submission.

Coronavirus 19 (COVID-19) Clinical Trial Guidance

During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Regulatory History:

We have had the following meetings/teleconferences with you:

- 01/16/2019 Guidance Teleconference
- 12/06/2017 Guidance Teleconference
- 09/06/2017 End-of-Phase 2 Meeting
- 12/14/2015 Type C Guidance Meeting

We have sent the following correspondences:

- 02/19/2020 Meeting Request – Written Responses
- 10/30/2019 Pediatric Study Plan – Written Response
- 11/09/2018 Pediatric Study Plan – Incomplete
- 04/12/2018 Advice/Information Request
- 04/20/2018 Advice/Information Request
- 03/01/2018 Advice/Information Request
- 06/21/2017 Breakthrough Therapy Designation Request Granted
- 08/04/2016 Advice/ Information Request
- 08/03/2016 Breakthrough Therapy Designation Request Denial
- 07/13/2016 Advice/Information Request
- 08/07/2017 Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

Question 16:
Pending receipt of the NDA, does the Agency agree that the proposed overall Table of Contents for the NDA is adequate and provides a complete application under the PDUFA VI program in support of filing a NDA?

FDA Response to Question 16:
The table of contents provided in Appendix 7 of your briefing package appears acceptable. A filing determination will be made by day 30 after NDA submission for a priority review.

Meeting Discussion:
The Agency confirmed that the filing notification will be sent by day 60.

Question 17:
Cara plans to submit a request for priority review at the time of submission of the NDA.

FDA Response to Question 17:
A priority review may be appropriate for applications with breakthrough designation. Determination of a priority review will be made at the time of the filing meeting.

Question 18:
Does the Agency plan to convene an advisory committee meeting for this NDA?

FDA Response to Question 18:
The Agency will discuss the need to convene an advisory committee meeting for difelikefalin during the initial review process and a determination will be conveyed in the filing communication.

2.2. Chemistry, Manufacturing and Control (CMC)

No CMC questions were provided for this meeting.

2.3. Nonclinical

Question 15:
Does the Agency agree that the scope of the nonclinical section is adequate to support the NDA filing and no additional nonclinical studies are required?

FDA Response to Question 15:
Your nonclinical program, which includes studies listed in Appendix 6 of the briefing document, appears adequate to support an NDA submission. The adequacy of the studies will be a review issue under the NDA.

2.4. Clinical Pharmacology

Question 13:
Based on the outcome of the pharmacokinetics and metabolism study of [14C] difelikefalin in patients with end stage renal disease on hemodialysis and healthy subjects, does the Agency agree that the question regarding metabolites in hemodialysis patients has been adequately addressed to support the NDA filing?

FDA Response to Question 13:
We acknowledge that you identified low level of metabolites in feces and urine from hemodialysis subjects. The adequacy of your metabolite profiling results will be a review issue at the time of NDA submission.

Question 14:
Does the Agency agree that the scope of the clinical pharmacology section is adequate to support the NDA filing and no additional studies are required?

FDA Response to Question 14:
Based on your summary table, the clinical pharmacology studies appear reasonable to support filing of your NDA. The adequacy of your clinical pharmacology studies will be a review issue at the time of NDA submission.

2.5. Clinical/Biostatistics

Question 1:
Does the Agency agree with the preferred terms included in the Custom MedDRA Queries for Adverse Events of Special Interest (AESIs)?

FDA Response to Question 1:
You state that the Standard MedDRA Query (SMQ) provided by MedDRA is too broad to capture the desired Adverse Events of Special Interest (AESI) in your clinical trials. As a result, you've created "Custom MedDRA Queries" (CMQ) to accommodate the safety evaluation. The CMQ strategy provided in Appendix 2 of your briefing package is acceptable. Safety data under PT terms need to be reviewed for proper category placement. Provide your CMQ code and the full safety database you applied the queries for verification.

Meeting Discussion:
The sponsor stated that multiple MedDRA versions were used to code the adverse events (AE) but will be standardized to common MedDRA version 22 for ISS AE evaluation. The Agency clarified that the ADAE SAS dataset is appropriate.

Question 2:
Based on a review of the current safety data provided in the briefing book in chronic kidney disease patients undergoing hemodialysis, does the Agency agree that the potential risks for IV difelikefalin can be managed through product labeling and routine pharmacovigilance surveillance for this patient population and a Risk Evaluation and

Mitigation Strategy (REMS) would not be required?

FDA Response to Question 2:
It is unlikely that a REMS will be required for the safe use of IV difelikefalin as a treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients undergoing hemodialysis based on our review of the summarized information contained in your meeting package. However, the final determination for necessity of a REMS depends on the overall risk benefit assessment of your application and will be decided after your complete application has been reviewed.

A complete review of the full risk management plan after the NDA is submitted will be necessary to determine whether the proposed approach is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

Question 3:
Does the Agency agree with Cara's approach regarding original coding variables in the ISS.ADAE structure?

FDA Response to Question 3:
Your approach regarding original coding variables in the ISS. ADAE structure is acceptable.

Pooling for safety data should follow your intended dosing regimen. The pivotal Phase 3 clinical trials should represent the main safety pooling strategy for review. A pooling of all your studies can be done for support purposes. It is preferable to select the most recent MedDRA version and evaluate all your studies by the selected version for consistency.

Question 4:
Does the Agency agree that the proposed content outline of the abuse potential section of the NDA is adequate to enable the Agency to develop its abuse potential assessment and drug scheduling recommendations and that no additional content is required?

FDA Response to Question 4:
In general, the outline you provided is consistent with the 2017 FDA guidance for industry, *Assessment of the Abuse Potential of Drugs*. However, the adequacy of content cannot be determined until the NDA is submitted. We do have one recommendation for an addition to the abuse potential section:

- Provide a chart comparing the plasma levels produced by the doses of difelikefalin used in animal abuse-related studies with the plasma levels of difelikefalin produced in humans at therapeutic and supratherapeutic doses.

Question 5:
Does the Agency agree with the proposed list for evaluating potential abuse-related AEs?

FDA Response to Question 5:
See FDA Response to Question 6.

Question 6:
Does the Agency agree with the proposed plan for evaluating potential abuse-related AEs?

FDA Response to Question 6:
Yes, we agree with the proposed list and proposed plan for evaluating abuse-related AEs in clinical studies conducted with difelikefalin, since they are based on the 2017 guidance for industry, *Assessment of Abuse Potential of Drugs*.

Question 7:
Does the Agency agree with the proposed plan for evaluating withdrawal-related AEs?

FDA Response to Question 7:
Yes, we agree with the proposed plan for evaluating withdrawal-related AEs in clinical studies conducted with difelikefalin, since it is based on the 2017 guidance for industry, *Assessment of Abuse Potential of Drugs*.

Question 8:
Does the Agency agree that the prespecified analysis of the human abuse potential study, CLIN1006, will be the primary analysis and the proposed additional post-hoc analysis (in line with the FDA guidance, “Assessment of Abuse Potential of Drugs”, January 2017) will be a supportive analysis?

FDA Response to Question 8:
The response to this question is pending on an internal consultation and will be included as a post meeting comment in the final meeting minutes.

Post-Meeting Comment:
We recommend that the primary analysis should be carried out following the 2017 FDA guidance “Assessment of Abuse Potential of Drugs” with your proposed margins stated in the meeting document. Your originally proposed analysis can be used as a supportive analysis. The primary analysis should be on the Completer Population and the analysis on the Modified Completer Population can be used as secondary analysis.

If Williams squares are completed at the end of the study, the Williams squares should balance the first-order carryover effects. However, the dropouts of subjects in the Treatment phase may lead to incomplete Williams Squares. Therefore, the first-order-carryover effect should be included in the mixed-effects model if the test for the first-

order-carryover effect is significant at 0.25 level. You need to report both p-value and the one-sided 95% confidence interval for each comparison of the primary analysis. For the primary comparison, you should also provide a two-sided 95% confidence interval for the difference between these treatments. This confidence interval will provide the information about the absolute difference between treatments.

Question 9:
Does the Agency agree with the definition of the analysis populations in study CR845-100303 and the possible modification to this definition to address the potential effects of COVID-19?

FDA Response to Question 9:
The response to this question is pending on an internal consultation and will be included as a post meeting comment in the final meeting minutes.

Post-Meeting Comment:
Yes. It is acceptable.

Question 10:
Does the Agency agree with the algorithm to address missing items responses in the COWS and SOWS questionnaires?

FDA Response to Question 10:
The response to this question is pending on an internal consultation and will be included as a post meeting comment in the final meeting minutes.

Post-Meeting Comment:
It is acceptable to apply this algorithm to each treatment group. You should also provide information about the adverse events along with the visit missing status of each subject during the withdraw period.

Question 11:
Does the Agency agree with the proposed primary and supportive analyses of the primary and secondary endpoints in study CR845-100303?

FDA Response to Question 11:
The response to this question is pending on an internal consultation and will be included as a post meeting comment in the final meeting minutes.

Meeting Discussion for Questions 8-11:
The Agency advised we cannot provide a response until completion of internal consultation.

As the internal consultation has since been completed, Post Meeting Comments are provided below.

Post-Meeting Comments:

(1) We do not agree your primary endpoint for this physical dependence study of difelikefalin. The primary endpoint should reflect the maximum score in COWS. We recommend the primary endpoint to be the peak response of COWS for each subject during the withdrawal period. The difference between the mean peak COWS scores of subjects in the two treatment groups should be used for evaluating the effect of physical dependence of difelikefalin using the prespecified clinically meaningful margin.

(2) The sample size should be adjusted with regard to the new primary endpoint.

(3) With the new primary endpoint, please specify the statistical method you will use for the analysis.

(4) Provide detailed plan to handle missing visits and dropouts in your Statistical Analysis Plan.

The Sponsor can submit additional questions that arise from the Agency response to the IND.

Question 12:

Can the Agency comment on the timeline for review activities associated with a scheduling recommendation for difelikefalin under the Controlled Substances Act?

FDA Response to Question 12:

During an NDA review, the abuse-related data are reviewed by the Controlled Substance Staff (CSS). If CSS determines that the drug has abuse potential and should be recommended for scheduling under the Controlled Substances Act (CSA), they will prepare a scientific and medical analysis of the drug's abuse potential in an "Eight Factor Analysis" (8FA). This document is responsive to the requirements of the Controlled Substances Act (CSA) and is prepared in conjunction with the National Institute on Drug Abuse (NIDA) on behalf of the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS).

The 2015 Improving Regulatory Transparency for New Medical Therapies Act ("the Act") streamlined the scheduling process by establishing time lines for DEA scheduling actions in relation to NDA approval actions. Under the Act, FDA approval of an NDA for a drug with abuse potential may not take effect until DEA issues an interim final rule under 21 U.S.C. 811(j) establishing a temporary scheduling placement for the drug, in accordance with 21 U.S.C. 355(x).

DEA has 90 days to publish the interim final rule in the Federal Register, once both of the following events have occurred (in any order): 1) FDA has approved the NDA and formally notified DEA of the approval, and 2) the 8FA for the drug has been transmitted

from the ASH to the DEA. Once the interim rule has been issued, the new drug applicant may update their product labeling to reflect the scheduling action (through supplement submission to their NDA) and then market their drug. Subsequently, DEA will issue a final rule that permanently places the drug under the CSA.

Question 19:
Does the Agency agree with the proposed plan for submission of the 4-month safety update?

FDA Response to Question 19:
You should take into consideration that if you are granted a priority review, your safety update should be provided to the Agency by month three, coincidental with the mid-cycle review.

Question 20:
Based on the Agency's Response to the Type B Meeting (written responses only), dated September 11, 2019, the Agency agreed with Cara's Proposal to provide full narratives for subjects who died, had other nonfatal SAEs, and other significant AEs including AEs leading to discontinuations and narratives for AEs of special interest from Phase 3 studies if there is a meaningful imbalance (≥1%) between difelikefalin and placebo. Cara will also provide case report forms (CRFs) for subjects who died, had other nonfatal SAEs, and other significant AEs including AEs leading to discontinuations and patient listings for AEs of special interest from Phase 3 studies if there is a meaningful imbalance (≥1%) between difelikefalin and placebo. Does the Agency agree with this proposal?

FDA Response to Question 20:
Your proposal is acceptable.

Additional Comments:
We refer you to previous Agency comments and recommendations regarding dataset submission and SAS code (i.e., see responses to Question 5 for meeting on January 16, 2019 and Question 6 in written responses dated September 11, 2019).

Meeting Discussion:
The Agency noted the preliminary Phase 3 study data presented by the sponsor. The Agency requested that the labeling proposal address a 4-point change in the worst itch NRS scale, as previously recommended, in several Agency communications. In addition, the Agency noted the higher placebo response rate in the second Phase 3 study and recommended the sponsor investigate the possible cause of this increase in the NDA.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[5]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical*

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENDALL A MARCUS
06/17/2020 10:47:54 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123140

MEETING MINUTES

Cara Therapeutics, Inc.
Attention: Edward Liao, PharmD
Head of Regulatory Affairs
4 Stamford Plaza, 9th Floor
Stamford, CT 06902

Dear Dr. Liao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for difelikefalin intravenous solution, 0.5 mcg/kg.

We also refer to the meeting between representatives of your firm and the FDA on September 06, 2017. The purpose of the meeting was to discuss the Phase 3 clinical development program for difelikefalin intravenous solution.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Pinakini Patel, Regulatory Project Manager at (301) 796-7475.

Sincerely,

{See appended electronic signature page}

Kendall Marcus, MD
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Handout

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 06, 2017 @ 11 a.m.
Meeting Location:	White Oak Campus
Application Number:	IND 123140
Product Name:	difelikefalin intravenous solution, 0.5 mcg/kg
Proposed Indication:	For moderate to severe pruritus associated with chronic kidney disease in hemodialysis patients
Sponsor Name:	Cara Therapeutics, Inc.
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Barbara Gould

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation (ODE) III
Hylton V. Joffe, MD, MMSc, Acting Deputy Director, ODE III
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Carmen Booker, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Jihye Ahn, PharmD/MS, Clinical Pharmacology Reviewer, DCP III
Donna Christner, PhD, Acting API Branch Chief, ONDP, OPQ
Hitesh Shroff, PhD, Acting Quality Assessment Lead, DNDP II, NDPB V
Selena Daniels, PharmD, MS, Team Leader, Clinical Outcomes Assessment (COA)
Michelle R. Iannacone PhD, MPH, Epidemiologist, Division of Epidemiology I
Katherine Bonson, PhD, Pharmacologist, Controlled Substance Staff
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES

Joseph W. Stauffer, DO, MBA, Chief Medical Officer, Cara Therapeutics, Inc.

Frédérique Menzaghi, PhD, VP, Research and Development, Cara Therapeutics, Inc.
Edward Liao, PharmD, Head of Regulatory Affiairs, Cara Therapeutics, Inc.
Catherine Munera, PhD, Head of Biometrics, Cara Therapeutics, Inc.
Robert Spencer, PhD, Sr. Director, Research and Development, Cara Therapeutics, Inc.
Stephen O'Connor, PhD, Sr. Director, Chemistry Research and Development, Cara Therapeutics, Inc.
(b) (4) Consultant, (b) (4)
(b) (4) Consultant, (b) (4)
(b) (4) Medial Monitor, (b) (4)
(b) (4) Consultant

1.0 BACKGROUND

Cara proposes to discuss with the Agency specific aspects of the clinical, nonclinical, and manufacturing development plan for CR845, as well as the appropriateness of the proposed plan to support the submission of a NDA for IV CR845 for the indication of relief of moderate- to-severe CKD-aP in HD patients.

2. DISCUSSION

Meeting Discussion:
The sponsor provided an extensive interim response to the Agency's preliminary meeting communication, which is appended to these meeting minutes. Not all of the sponsor comments could be addressed during the meeting due to time constraints. The meeting discussion noted in the meeting minutes reflects in part the sponsor comments in this interim submission. The sponsor noted that they would submit additional information to the IND related to the additional analyses included in the interim submission.

The Agency stated at the beginning of the discussion that there are notable safety issues, at least some of which were likely related to the investigational product. The relationship of these events to the product may be of more concern than acknowledged in the briefing document. The Agency recommended that safety events be assessed in the aggregate in subjects with complex medical histories. The Agency noted that the program should adequately demonstrate an adequate risk/benefit profile for the proposed indication.

The Agency agreed with the sponsor proposal to prospectively assess adverse events of special interest, and recommended that the revised protocol include prospective assessment of CNS related events such as mental status changes, somnolence, and dizziness, particularly since the product is a kappa opioid agonist.

2.1. CHEMISTRY, MANUFACTURING, AND CONTROLS

Question 20:
Does the Agency agree that Cara has provided adequate information regarding CR845 drug substance to address the following outstanding concerns raised in the Type C meeting initial response?

a. The change in acceptance limit for [redacted] from [redacted]% to [redacted]% for commercial drug substance;

b. Acceptability of using the summation method found in USP <232> (API + excipients) and the projected commercial dose (0.5 mcg/kg for CR845 drug product) for establishing the elemental impurity limits for the CR845 API; and

c. Adequacy of the completed preparation and characterization of all [redacted]

FDA Response:

a. No, [redacted] revise the acceptance limit to NMT [redacted]%.

b. Yes, the method for setting elemental impurity limits for the API appears acceptable.

c. No, explain [redacted]

Meeting Discussion;
The Agency agreed that the information provided in the addendum concerning [redacted] is acceptable. Therefore, FDA Response c is acceptable.

Question 21:
Does the Agency agree that for the [redacted] facility:

a. [redacted]

b. The submission of stability data from storage for at least 12 months at long-term, 12 months at intermediate-term, and six months at accelerated conditions from the three batches above will be adequate to assign a [redacted] month expiry date?

FDA Response:

a. Your proposal is not acceptable. [redacted]

Meeting Discussion:

(b) (4)

b. The amount of stability data proposed to be included in your NDA submission appears reasonable to be used for determination of expiration dating period of the drug product provided that the 3 registration batches of the drug product are manufactured using the commercial production process (See above response). The expiration dating period of the drug product will be determined during NDA review based on stability data submitted in your NDA.

Question 22:

Does the Agency agree that for the (b) (4) facility the submission of stability data from storage for at least 12 months of long-term, 12 months of intermediate-term, and 6 months of accelerated conditions (from the manufacture of three registration batches at full commercial scale) will be adequate to assign a (b) (4) month expiry date?

FDA Response:

The stability data obtained from 3 full-scale registration batches, which are to be manufactured according to the commercial production process and planned to be included in your NDA submission, appears reasonable to be used for determination of expiration dating period of the drug product. The expiration dating period of the drug product will be determined during NDA review based on stability data submitted in your NDA.

Question 23:

Does the Agency agree that the drug product manufacturing and release data provided from (b) (4) and (b) (4) demonstrate that drug product manufactured by both facilities are comparable and that both sites are suitable to manufacture commercial CR845?

FDA Response:

Comparability of the drug product batches manufactured at the two proposed manufacturing sites cannot be established based on the information provided in the briefing package. The (b) (4) (b) (4) of the drug product from these two sites were not the same (b) (4) and the amounts of data provided are not adequate. At least 3 months of long-term and accelerated stability data from at least 3 pilot-scale batches of the drug product manufactured at each of the two proposed manufacturing sites should be provided to establish comparability of the drug product batches manufactured at the two proposed manufacturing sites. Additionally, compatibility between the drug and the surface of the preparation equipment and containers (b) (4) and extractable/leachable impurities from the preparation equipment and containers should be evaluated. The evaluation results should be provided in your NDA submission.

2.2. CLINICAL PHARMACOLOGY

Question 14:
Because of the availability of PK data from our Phase 1 and 2 studies with hemodialysis patients, and the frequent difficulties and safety concerns in collecting PK blood samples in this patient population:

a. Does the Agency agree that neither conventional nor sparse (population) pharmacokinetic sampling will be required in the Phase 3 studies?

b. Does the Agency agree that no further human PK studies are required to support the filing of the NDA in support of the pruritus indication?

FDA Response:
We acknowledge the challenges of obtaining PK samples in subjects on hemodialysis. Your plan of not assessing pharmacokinetics (PK) in the Phase 3 trial(s) appears reasonable.

Since you had large number of aberrant systemic concentrations, in your NDA we recommend you to submit PK analysis by including and excluding all the concentrations that you consider aberrant. In addition, the systemic concentrations that you choose to exclude as being aberrant should be accompanied by a justification for each of them.

Depending on the results of the proposed ADME study in hemodialysis subjects, additional clinical pharmacology studies might be needed.

Question 15:
Does the Agency agree with the proposed study design of the human ADME/metabolism study (CR845-CLIN1302)?

FDA Response:
We acknowledge your plan to conduct an ADME/metabolism study in subjects on dialysis as well as in heathy subjects and your proposal appears reasonable. However, since there were many aberrant systemic concentrations observed in earlier pharmacokinetic trials, you should make every effort towards producing good quality data.

Question 16:
Does the Agency agree that the existing *in vitro*/nonclinical DDI studies, along with the observation that no DDI-related issues have emerged to date in any clinical trials of CR845, either in patients on dialysis or other populations, demonstrate that:

a. there is no need to include restrictions of concomitant medications in the Phase 3 studies?

b. If no major metabolites (≥10%) are identified in the proposed human ADME study (CR845-CLIN1302), then no further *in vitro* or *in vivo* DDI studies are necessary to support the submission of a NDA for CR845 for the proposed pruritus indication?

FDA Response:
Based on the summary of in-vitro drug interaction information you have provided, your plan to not have any restrictions of concomitant medications in the Phase 3 trial(s) appear reasonable.

If no major metabolites are identified in the proposed human ADME study, then further drug interaction assessments would not be needed.

2.3 NONCLINICAL

Question 18:
Does the Agency concur that submission of the 2-year carcinogenicity study report subsequent to NDA submission and marketing approval is acceptable?

FDA Response:
No, we do not concur. The final 2-year carcinogenicity study report should be included in the NDA submission. If the final 2-year carcinogenicity study report is not included in the NDA submission, then this will be a filing issue.

To enable us to conduct the statistical review of final carcinogenicity study reports, submit SAS tumor data sets (tumor.xpt) for each carcinogenicity study in the NDA submission. Follow the standard format provided in the table below for preparing the data.

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

Question 19:

Does the Agency agree that since no toxicology studies were initiated on or after December 18, 2016 and no additional toxicology studies are planned, Cara will not be required to submit any studies in the SEND format for the NDA?

FDA Response:
Yes, we agree.

2.4 CLINICAL and NONCLINICAL

Question 17:
Does the Agency agree that the currently available clinical and nonclinical abuse potential data are adequate to assess the abuse/dependence risks posed by CR845 and provide scheduling recommendations? Specifically:

a. Does the Agency agree that the human abuse potential (HAP) study conducted with CR845 is adequate and that no additional clinical abuse potential studies are required to support an NDA for the proposed indication?

b. Does the Agency agree that the nonclinical abuse studies are adequate to characterize the abuse potential for CR845 and no additional nonclinical abuse liability studies are required to support an NDA?

c. Does the Agency agree that the HAP clinical trial, in conjunction with the nonclinical abuse potential studies, are adequate for the Agency to conduct an abuse potential assessment and provide scheduling recommendations?

FDA Response:

a. In May 2014 and April 2015, CSS provided feedback on the protocol for the human abuse potential study with CR845. As we previously informed you, it is a review issue as to whether the design of this completed study appropriately incorporated our recommendations. Review of the full study report for the human abuse potential study will not occur until the NDA for CR845 has been submitted.

   We do not agree with your statement in the meeting package that the assessment of physical dependence may be satisfied with the completed animal studies. Given that CR845 is a new molecular entity with kappa opioid agonist activity, it will be necessary to evaluate the ability of CR845 to produce physical dependence in humans. This may be accomplished by adding a two-week discontinuation period at the end of a Phase 3 study. CSS is available to provide feedback on the design of the human physical dependence evaluation.

b. In April 2015, CSS informed you that we were available to provide feedback on the design of the self-administration, drug discrimination and physical dependence studies in animals. However, these studies were initiated and completed without prior CSS feedback. Thus, the adequacy of these studies is a review issue following submission of the NDA for CR845. In order to evaluate these studies, we will need pharmacokinetic information regarding the plasma levels produced by each dose via the route of administration used in the study. These data may be obtained from other already-

conducted studies. The animal plasma levels should be presented in relation to the plasma levels produced by the highest proposed therapeutic intravenous dose.

c. Refer to Section 2.4 Clinical and Nonclinical FDA Response for Question 17 a and b.

Meeting Discussion:
The Sponsor agreed to the recommendation from CSS that a 2-week discontinuation period be added to the Phase 3 clinical study so that physical dependence could be assessed. Although they will submit a complete protocol soon, they wanted to know if assessing adverse events, body temperature and vital signs would be adequate for this assessment. CSS replied that they needed to use standardized questionnaires specific to opioid withdrawal symptoms. It was agreed that the Clinician's Opioid Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS) would be considered, although the Sponsor also proposed the Objective Opioid Withdrawal Scale (OOWS). CSS said they would consider all proposals as long as they were justified. CSS also recommended that the Sponsor focus on withdrawal-associated AEs that are specific to discontinuation of kappa opioid agonists, rather that solely evaluating AEs that typically occur with mu opioid agonists.

The Sponsor additionally asked whether CSS would accept completed preclinical abuse-related studies that a) did not use both sexes of animals and b) did not conduct the studies under GLP (but were conducted with "the spirit of GLP"). CSS replied that although the new Guidance for Industry: Assessment of the Abuse Potential of Drugs (2017) did state that both sexes should be used in these studies and that GLP was to be used, we would waive these requirements on this occasion since the studies were already completed. However, any future drug development should conform to these guidelines.

CSS also agreed with the FDA clinical team that AEs should be assessed prospectively during drug administration, rather than leaving AE assessment to spontaneously provided statements by the patients. CSS recommended that the Sponsor create a list of AEs that are known to be associated with kappa opioid agonists, and that patients can be asked about these AEs at least at Cmax if not more frequently.

2.5 CLINICAL and STATISTICAL

Introductory Comments:

Our understanding is that your Phase 2 program includes 181 uremic pruritus subjects treated with your intravenous investigational product to date. The clinical treatment effects appear to be modest and lack dose response across the three dosing regimens assessed at eight weeks of treatment. While this preliminary clinical evidence was deemed sufficient to grant Breakthrough Designation for your development program for uremic pruritus, we cannot provide agreements on basic elements of your Phase 3 program as we have safety concerns that require further discussion.

The cumulative safety data collected in the hemodialysis patient population raises concern for significant CNS impacts potentially resulting in serious adverse events such as gait disturbance,

falls, dizziness, somnolence, seizures, and syncope. Additionally, tachycardia and palpitations were observed and presumably cannot be attributed to free-water diuresis in this patient population. Be prepared to discuss these events at the upcoming meeting including ways these events could be carefully assessed and mitigated in a future study (e.g., evaluating a dose less than 0.5 mcg/kg). We remind you that prospective development of a plan for assessing serious adverse events and other important safety information is a critical component of a premarket safety system for IND safety reporting. Sponsors should develop a safety surveillance plan that describes processes and procedures for assessing serious adverse events and other important safety information (see guidance for industry, *Safety Assessments for IND Safety Reporting*).

Note that the standard for approval of drugs for treatment of indications with a Breakthrough Designation is the same as for drugs without such designation. That is, substantial evidence of clinical benefit/effectiveness, safety and product quality will need to be demonstrated. "Substantial evidence" has been defined in the Food, Drug and Cosmetic Act as: "evidence consisting of adequate and well-controlled (A&WC) investigations… on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use…" This has generally been interpreted as evidence from at least two A&WC trials. If a single trial is to be relied on to support effectiveness, this trial should be appropriately designed, be of sufficient size and/or rigor to produce results that are statistically persuasive and clinically meaningful, and/or demonstrate internal consistency (such as multiple endpoints involving different events demonstrating beneficial effects), among other considerations. Refer to the guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* for additional discussion about relying on a single study to provide evidence of effectiveness. The reliance on a single A&WC trial will be a matter of review judgment and will be considered in the context of the disease and the trial results. The results would need to be statistically robust and consistent across subgroups and centers, among other criteria. For robust statistical findings, the trial should be powered for the recommended primary endpoint (i.e., a responder endpoint, see below) using a two-sided α much less than the customary 0.05.

Meeting Discussion:
The sponsor inquired whether a two-sided α of 0.025 would lead to robust statistical findings. The Agency responded that they would expect an α much less than the proposed 0.025 to be used for powering the Phase 3 trial as well as the statistical analysis thereafter. The Agency noted that a small p value is just one component of robust statistical findings including consistency across subgroups and centers.

The following are comments regarding the submitted protocol for your proposed Phase 3 trial:

- You plan to conduct an interim analysis for sample size re-estimation after 50% to 60% of the 300 randomized subjects either complete the 12-week treatment period or discontinue study drug prematurely. The complete details of this interim analysis were not provided but you stated that additional details on the interim assessment process will be included in the IDMC charter. Details such as timing, thresholds, and methodology should be completely pre-specified and submitted to the Agency for review prior to initiating the trial. In addition to potentially inflating the Type I error rate, adaptations such as sample size modification

may induce biases in estimates of the treatment effect and decrease the coverage of confidence intervals. The draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* identifies as a principal issue "whether the adaptation process has led to positive study results that are difficult to interpret irrespective of having control of type I error." The guidance also notes that the documentation for an adaptive adequate and well-controlled trial should include "a summary of each adaptation and its impact upon critical statistical issues such as… parameter estimates and confidence intervals..." You have not provided enough information to evaluate the potential impact of the proposed adaptations on the properties of statistical inference at the end of the trial. You should evaluate this impact and justify your approach to reliably estimate the treatment effect. We also note that your interim analysis would need to take into account your proposal to conduct a single Phase 3 trial (i.e., a two-sided α much less than the customary 0.05)

Meeting Discussion:
The sponsor acknowledged the Agency comments regarding the interim analysis and stated that they will submit an amended protocol and the IDMC charter which will address the Agency's comments.

- The proposed primary efficacy endpoint is change from baseline to Week 12 in the Worst Itching Intensity Numeric Rating Scale (NRS) score. In your meeting package and your Breakthrough Therapy Designation application, you stated that a decrease of 2.47 points on the Worst Itch Intensity NRS would represent a meaningful change, and this determination was based on data from your completed Phase 2 trial (CR845-CLIN2101) using anchor-based methods. As stated in previous communications, the recommended primary efficacy endpoint is the proportion of subjects who achieve a clinically meaningful change (i.e., responder definition), see FDA Response to Question 11.

Meeting Discussion:
There was general discussion about defining the primary endpoint and the success criterion. The Agency clarified that the primary endpoint should be based on a responder definition, which is based in change from baseline to Week 12 with a threshold level of 4 point change. The sponsor advocated using a 2 point change. The Agency responded that the mean change for subjects in the placebo arm from your Phase 2 trial was 1.9. The Agency proposed that the sponsor may submit data from their clinical trials to support their argument of using a lower threshold level than the Agency recommended 4 point change. The sponsor should also provide a rationale for anchoring the worst itch intensity NRS to the PGIC "minimally improved" anchor response category.

- You propose to analyze the primary efficacy endpoint using a mixed effect model for repeated measures (MMRM). It should be noted that the results from an approach that incorporates information from each visit might not be clinically meaningful yet the analysis might yield a statistically significant treatment effect due to the incorporation of all of the data. As efficacy is to be established at Week 12, your analysis should be based specifically on the Week 12 data; however, modeling approaches using all time-points may be used as supportive/sensitivity analyses.

- You protocol specifies three secondary efficacy endpoints along with a gatekeeping strategy to control the Type I error rate. Specifically, your protocol specifies that although the p-values corresponding to the hypothesis testing of the secondary endpoints will be reported, they will only be considered inferential if the analysis of the primary endpoint is statistically significant. However, in your meeting package, you stated "since the secondary variables will only provide supportive evidence of efficacy, no adjustment for multiple testing is planned." Secondary endpoint intended for labeling should be limited in number, clinically meaningful and analyzed with appropriate multiplicity control. In addition, you would need to take into account your proposal to conduct a single Phase 3 trial (i.e., a two-sided α much less than the customary 0.05).

- As there is no universally appropriate method for handling missing data that can occur in clinical trials, we recommend designing and conducting the trial in such a way to minimize the occurrence of missing data. The efficacy analyses should be based on the intent-to-treat (ITT) population (i.e., all randomized subjects) and your protocol should pre-specify a scientifically sound primary imputation method (e.g., multiple imputation) to handle missing data. In addition, the protocol should pre-specify sensitivity analyses that utilize alternate assumptions to those in the primary imputation method to ensure that the results are not driven by the method of handling missing data.

Meeting Discussion:
The sponsor proposed to use multiple imputation as the primary imputation method. The Agency responded that this may be reasonable provided that the full details are specified in the protocol.

Question 1:
Considering the positive and clinically significant results of the supportive studies, CR845-CLIN2005 and CR845-CLIN2101-Part A, the unmet medical need for uremic pruritus, and the recent designation of CR845 as a breakthrough therapy, does the Agency agree that one positive, pivotal Phase 3, 12-week randomized, placebo-controlled, safety and efficacy study (CR845-CLIN3102), along with two open-label long-term safety studies, one of which will enroll *de novo* patients not previously exposed to CR845, will be adequate to support an NDA for the proposed indication?

FDA Response:
See Section 2.5 Clinical and Statistical, Introductory Comments. As previously advised, two adequate and well controlled trials are recommended for your development program.

Question 2:
Does the Agency agree that considering the unmet medical need for uremic pruritus and the current safety profile of CR845, a safety database of approximately 1000 total exposures, with approximately 300 hemodialysis patients with uremic pruritus exposed for 6 months and approximately 100 hemodialysis patients with uremic pruritus exposed for 1 year, is adequate to support an NDA?

See Section 2.5 Clinical and Statistical, Introductory Comments. Your safety database currently includes approximately 213 hemodialysis patients who have received single or repeated IV injections of CR845 for up to 8 weeks ranging from 0.5 to 6 mcg/kg across two Phase 1 and two Phase 2 (CR845-CLIN2005 and CR845-CLIN2101-Part A) studies. Your proposed Phase 3 clinical trial (CR845-CLIN3102) will include a maximum of 400 subjects (randomized 1:1), limiting exposure to approximately 413 hemodialysis patients. The safety of your proposed product will need to be better characterized prior to agreement on the size of the safety population.

Question 3:
Does the Agency agree that the safety database of approximately 1000 total exposures may include some of the following subjects:

- HD patients exposed more than once to CR845 who could be counted as 2 different exposures in the Integrated Summary of Safety in an NDA, if the interval between each exposure is > 1 month;

- HD patients with moderate-to-severe uremic pruritus who did not previously participate in a randomized, placebo-controlled CR845 clinical trial (i.e., *de novo* patients) and who could constitute up to 40% of the total exposures;

- *De novo* HD patients with mild uremic pruritus who could constitute a proportion (up to 20%) of the total exposures; and

- Patients who received the oral tablet formulation of CR845 if enrollment of HD patients with uremic pruritus into the long-term safety trials is more difficult than expected?

FDA Response:
See Section 2.5 Clinical and Statistical, FDA Response to Questions 3.

While the safety experience of CR 845 across all indications will be considered during the review of your application, your safety database should be sufficient to justify the safety of your proposed product for the proposed indication, which is for moderate to severe pruritus in hemodialysis patients.

- Individual subjects with varying exposures cannot count as multiple subjects for the purposes of satisfying E 1a recommendations for safety regardless of interval washout periods.

- Inclusion of long term safety study subjects who did not participate in randomized pivotal trials in the safety database is acceptable. However, differences in medical practice/hemodialysis treatment regimens in European study sites and their impact on safety outcomes would have to be addressed in the NDA submission.

- Inclusion of subjects with mild uremic pruritus (< itch intensity NRS of 4) would not be appropriate as this is not the indication sought for the development program. The risk benefit for mild pruritus needs to be considered in light of the safety findings to date. There appears to be adequate incidence of hemodialysis subjects with moderate to severe pruritus to achieve enrollment objectives to achieve E 1a recommendations.

- We recommend that adequate numbers of subjects treated with your proposed intravenous presentation be included in the NDA submission without reliance on other presentations currently under development.

Question 4:
Does the Agency agree that at the time of the NDA submission, Cara could provide the safety profile of 200 HD patients with pruritus exposed for 6 months and 50 HD patients exposed for one year to CR845, and the remaining 100 exposures of 6 months and 50 exposures of one year duration as a post-marketing commitment?

FDA Response:
No. Your application which demonstrates the safety and efficacy of your proposed treatment regimen should be complete at the time of NDA submission in order for the Agency to appropriately consider the safety and efficacy of your product. Your enrollment proposals appear insufficient given the nearly half million hemodialysis patients in the United States. The patient recruitment challenges appear surmountable to achieve E 1a guidance recommendations.

Question 5:
Does the Agency agree with the proposed (a) patient population, (b) general study design, and (c) dose and dosing regimen to be studied in the pivotal Phase 3, randomized, placebo-controlled study, CR845-CLIN3102, as described in the protocol?

FDA Response:
No. See Section 2.5 Clinical and Statistical Introductory Comments.

Question 6:
Based on the exceedingly low incidence and prevalence of uremic pruritus in the pediatric population, does the Agency agree that a waiver for PREA is justified?

FDA Response:
Submit your request for waiver, supporting data which substantiates the incidence and prevalence across the pediatric populations, and rationale, and the Agency will make a determination following review of your initial Pediatric Study Plan.

Refer to the Type C meeting between your firm and the FDA on December 14, 2015:

Be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan

to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*
at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

Question 7:
Does the Agency agree with the proposed sample size for the pivotal Phase 3 study?

FDA Response:
See Section 2.5 Clinical and Statistical Introductory Comments.

Question 8:
Does the Agency agree with the choice and proposed primary statistical analysis of the primary efficacy endpoint in the pivotal Phase 3 study?

FDA Response:
See Section 2.5 Clinical and Statistical Introductory Comments.

Question 9:
Does the Agency agree with the proposed sensitivity analyses of the primary efficacy endpoint in the pivotal Phase 3 study?

FDA Response:
See Section 2.5 Clinical and Statistical Introductory Comments.

Question 10:
Does the Agency agree with the choice and proposed statistical analysis of the secondary endpoints in the pivotal Phase 3 study?

FDA Response:
See Section 2.5 Clinical and Statistical Introductory Comments.

Question 11:
Does the Agency agree that an improvement from baseline with respect to the Worst Itching Intensity Score that is ≥ 30% is clinically significant?

FDA Response:
See Section 2.5 Clinical and Statistical Introductory Comments.

We generally recommend that you use anchor-based method supplemented with both cumulative distribution function (CDF) and probability density function plots to determine the threshold(s) for meaningful change in your instrument(s). We encourage you to use your Phase 2 data to perform these analyses, if possible, to help inform your responder threshold.

We acknowledge the anchor-based method results and CDF plots you provided in your breakthrough therapy designation package, dated April 21, 2017. You should also provide the following for review:

- Anchor-based methods—complete data tables of results for all response categories of the anchors (both worsening and improvement).

- Exact copies of the anchors administered (e.g., Patient Global Impression of Change [PGI-C], Patient Global Impression of Worst Itch Severity [PGI-S]).

- Final quantitative summary report, when available.

- Provide the following CDF and PDF plots, including sample sizes for each CDF and PDF curve in each plot's legend, and median scores for each CDF and PDF curve. Adjacent anchor response categories can be collapsed if the sample size within a particular anchor response category is small (with justification provided); however, you should submit both the non-collapsed and collapsed plots. Examples of CDF and PDF are provided at the end of the document in Additional Comments (See comments 20 and 21):

    - CDF and PDF plots of the Worst Itching Intensity NRS change scores from baseline to Week 8 for all patients by the different anchor response categories of the PGI-S at Week 8.

    - CDF and PDF plots of the Worst Itching Intensity NRS change scores from baseline to Week 8 for all patients by the different anchor response categories of the PGI-C at Week 8.

    - CDF and PDF plots of the Worst Itching Intensity NRS change scores from baseline to Week 8 for all patients with separate curves for the different score point changes (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.) in the PGI-C from baseline to Week 8.

- CDF and PDF plots of the Worst Itching Intensity NRS change scores from baseline to Week 8 by treatment arms (i.e. treatment vs. placebo).

Question 12:
Does the Agency agree with the proposed hypothesis testing strategy of the primary and secondary efficacy endpoints?

FDA Response:
See Section 2.5 Clinical and Statistical Introductory Comments.

Question 13:
Does the Agency agree with the proposed study data standardization approach for studies to be included in the NDA submission for this indication?

FDA Response:
For your Phase 2 and Phase 3 trials, your proposal to submit tabulation data in SDTM 1.4 format and analysis data in ADaM 2.1 format appears reasonable.

Additional Comments—Clinical Outcome Assessments
We acknowledge your efforts to capture patient-reported data to characterize clinical benefit in your planned clinical trials. You propose multiple patient-reported outcome (PRO) assessments. We recommend you consider limiting the number of assessments in order to reduce respondent burden, as there might be some measurement redundancy (e.g., Skindex-10 and 5-D Itch scale both measure the associated impacts of itch). Instruments should be selected that are best supported by available data and most closely adhere to the principles laid out in the 2009 Guidance for Industry on Patient Reported Outcome Measures. In some cases, subscales or items from existing instruments could be utilized if prospectively defined and in compliance with the instrument's user manual.

See our specific comments in regards to the proposed instruments:

Worst Itch Intensity NRS

1. A single item 11-point numeric rating scale, in principle, is fit for purpose to assess itch intensity.

2. You have not provided sufficient evidence to support the proposed threshold for meaningful change (i.e., >30% reduction) in your target population. See FDA response to Question 11.

Skindex-10

3. The instrument items query patients' "bother." Bother can be a challenging concept to measure and it can vary as a function of disease stage and individual tolerance. For example, patients may report being bothered by a symptom or impact that is not very severe, or alternatively, a patient may become tolerable to a symptom or impact and report less "bother" even though the symptom or impact remains severe. Further, different patients may have different levels of perceived bother with the same level of

symptom or impact intensity. Because of these challenges, symptom intensity or frequency might be more sensitive to treatment effect than the concept of bother.

4. Provide more details on scoring algorithm.

5. The use of a total score for this instrument may be problematic as it includes items that measure both symptoms and impacts, making it difficult to interpret the score and describe clinical benefit. We recommend that you examine your phase 2 data to evaluate whether the domains/ items of this instrument contribute similarly to the change in the total score and to understand which domains/items may be driving the result. Improvement in the total score should reflect general improvement in most items/domains to avoid labeling implications (i.e., misleading claims).

6. We recommend that you propose and justify a threshold for a meaningful score change in the Skindex-10 to help with interpretation of your study results. Refer to FDA response to Question 11 in regards to the recommended approach for determining a threshold for meaningful change.

7. Regulatory utility for labeling is unclear at this time.

5-D Itch Scale

8. The 2-week recall period will require patients to rely on their memory. Response is likely to be influenced by the patient's state at the time of recall. For these reasons, items with short recall periods or items that ask patients to describe their current or recent state are usually preferable.

9. Refer to FDA comments 4 and 5.

10. We recommend that you propose and justify a threshold for a meaningful score change in the 5-D Itch scale to help with interpretation of your study results. Refer to FDA response to Question 11 in regards to the recommended approach for determining a threshold for meaningful change.

11. Regulatory utility for labeling is unclear at this time.

Patient Global Impression of Change

12. In general, we view global ratings as exploratory measures that can be used as anchors for determining what constitutes a clinically meaningful change in another measure.

13. Regulatory utility for labeling is unclear at this time.

Patient Self-categorization of Pruritus Disease Severity

14. Clarify the intent of use for this measure. We generally recommend the use of a static, current state global impression of severity scale for use as an anchor, which is administered throughout the study.

15. The design of this measure seems complex and might not be well understood by patients. If you proceed to use a patient global impression of severity (PGIS) scale, we recommend that you simplify this scale. An example of a simple PGIS is as follows:

    Patient Global Impression of Severity (PGI-S) Example:

    Please choose the response below that best describes the severity of your <SYMPTOM/OVERALL STATUS/ETC> over the past week.

    - ❑ None
    - ❑ Mild
    - ❑ Moderate
    - ❑ Severe

General comments regarding PRO measurement strategy:

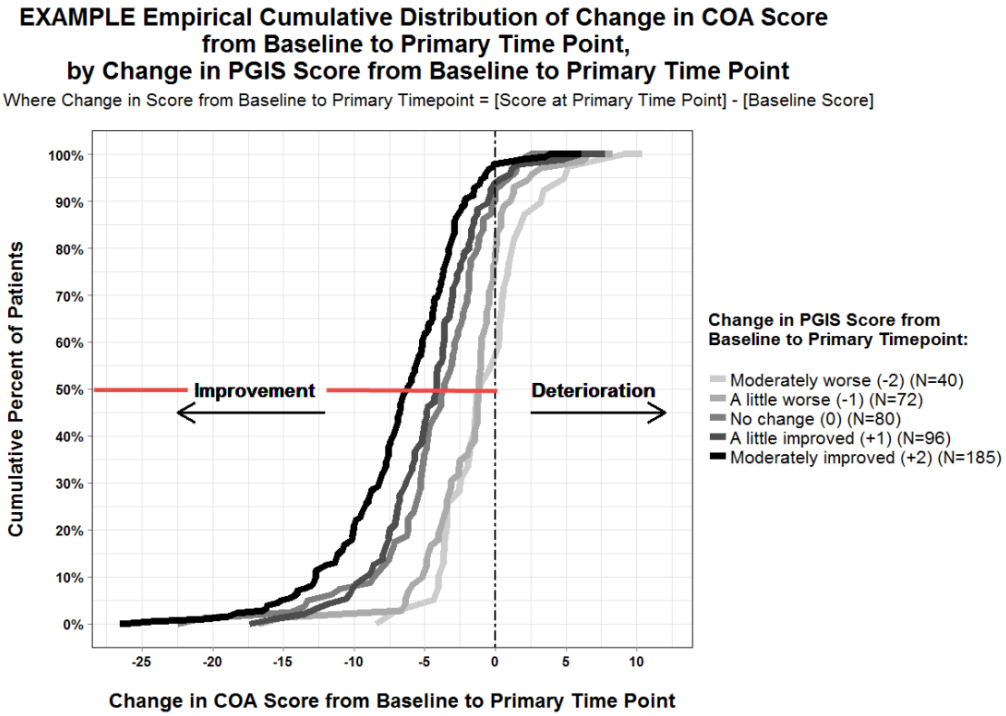
16. Inclusion of PRO data in the product label will depend on the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial.

17. You have provided a representation of the content of the proposed instruments. Please submit exact copies of the instruments, as they will be administered during the clinical trial(s) and any training materials and user manuals for review.

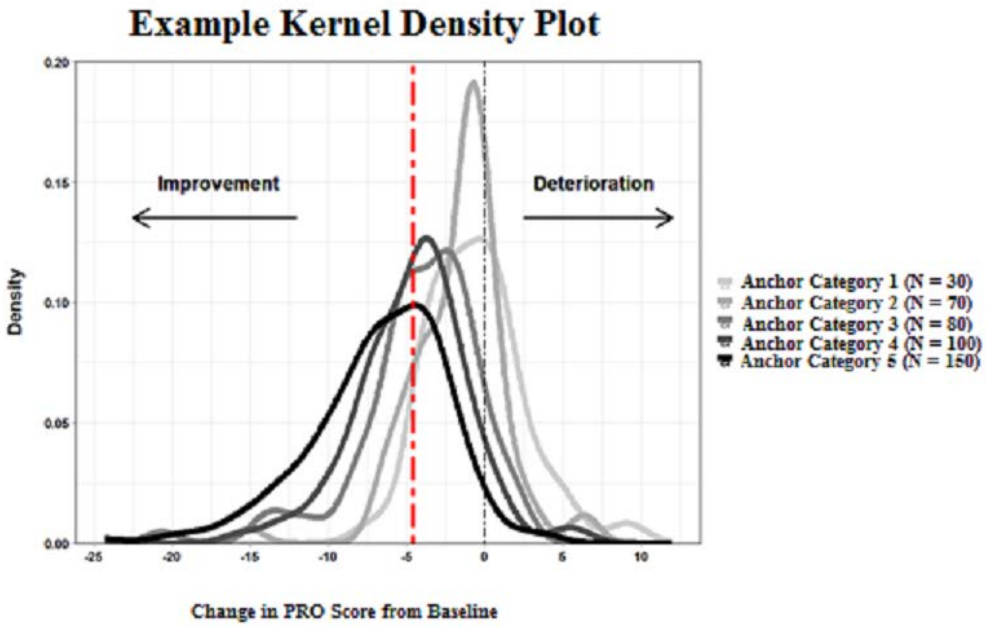
18. The schedule frequency of assessments should correspond with the length of recall of the instrument.

19. When appropriate and feasible, we recommend electronic data capture using a device with a reminder or alarm function as this tends to facilitate operation, minimize the extent of missing data and allows for the collection of other important information (e.g., timestamps for data input). You may refer to the FDA Guidance for Industry on electronic source data. If you proceed with electronic data capture, we recommend you perform usability testing of the selected devices and implement a back-up plan (e.g., paper, web- or paper-based) in case of any malfunctions with the electronic devices, prior to using the devices in your Phase 3 trials.

20. Example of CDF Plot:



21. Example of PDF Plot:



3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of

IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

COMPOUNDED DRUG PRODUCT REQUIREMENTS

As described at 21 CFR 210.2(c), a drug product, including a compounded product, intended for use in a clinical study must be prepared in accordance with the current good manufacturing practice requirements appropriate for the product. For questions or clarification, contact Compounding@fda.hhs.gov.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do

not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

4.0 ATTACHMENTS AND HANDOUTS

- Caro's response to Agency's preliminary responses

28 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
10/11/2017

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 123140
Request Receipt Date	21-APR-2017
Product	CR845 intraveneous injection
Indication	Moderate to severe pruritus associated with chronic kidney disease in hemodialysis patients
Drug Class/Mechanism of Action	A peptide agonist that binds to the kappa opioid receptor in humans
Sponsor	CARA Therapeutics
ODE/Division	ODE3/Dermatology and Dental Products
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	20-JUN-2017

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Moderate to severe pruritus associated with chronic kidney disease in hemodialysis patients

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
        - i. Only animal/nonclinical data submitted as evidence ☐
        - ii. Insufficient clinical data provided to evaluate the BTDR

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

CARA Therapeutics, Inc. submitted an initial breakthrough therapy designation (BTD) request on 14-JUN-2016 for relief of moderate-to-severe prutitus associated with chronic kidney disease in hemodialysis patients. The Agency reviewed the available data for the BTDR and the Division denied the request on 3-AUG-2016. The letter cited the following rationale:

(b) (4)

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

(b) (4)

(b) (4)

This current submission from CARA is the second request for BTD. The sponsor reports completing and presenting the analysis of clinical study CR845-CLIN2101, an 8-week dose-ranging Phase 2 study in hemodialysis patients with moderate-to-severe pruritus. According to the sponsor, the data from CR845-CLIN2101 provides sufficient clinical evidence to satisfy the required improvement over available therapies.

The sponsor opened IND 123140 with a protocol for a Phase 2 clinical trial (CR845-CLIN2005), titled "A Double-Blind Randomized, Placebo-Controlled Study to Evaluate the Safety and Pharmacokinetics of Intravenous CR845 in Hemodialysis Patients, and its Safety and Efficacy in Hemodialysis Patients with Uremic Pruritus." The proposed trial consists of two parts: Part A (1 week for PK; 24 subjects) and Part B (2 weeks for safety and efficacy; 30 subjects on placebo and 30 subjects on CR845 1 mcg/kg). This protocol was found "Safe to proceed" by the Agency on 7-AUG-2014. Subsequently, the sponsor met with the Agency on 14-DEC-2015 for an End-of-Phase 2 meeting with the summary results of the completed Phase 2 clincial trial (CR845-CLIN2005). The Agency provided several recommendations on PRO endpoints and the proposed development program. In particular, the Agency recommended the sponsor to use a responder analysis instead of mean change from baseline, as interpretation of mean change is problematic and would unlikely be acceptable. Post the EOP2 meeting, the sponsor submitted a protocol for a Phase2/3 clinical trial (CR845-CLIN2101). This is a two-part clinical trial with a 8-week (Part A; dose-ranging) and a 12-week (Part B; single dose) treatment period. The results of the 8-week analysis is the data for which the BTDR is based. The 12-week portion of the protocol will not start until after anther EOP2 meeting is held with the Agency.

CR845 is reported to be a potent and selective agonist at the human kappa opioid receptor being developed for the treatment of acute pain, chronic pain, and pruritus. Opioid receptors consist of three subtypes, mu, kappa, and delta, which are all involved in the modulation of pain and itch. These subtype receptors are found in the central nervous system (CNS, i.e. brain and spinal cord), in peripheral tissues (PNS, such as skin and viscera), and in the immune system. CR845 activates the kappa receptors, unlike morphine, which activates primary the mu receptor. The difference is the side effects of reducing sedation, respiratory suppression, euphoria, and constipation. The kappa receptors are known to modulate pain, itch, and inflammation. CR845 is also less CNS activating due to limited membrane permeability.

(b) (4)

7. Information related to endpoints used in the available clinical data:

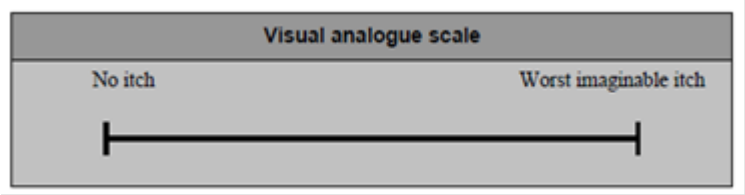
a. A Brief description of CR845-CLIN2005, which was the randomized, multicenter, double-blind, placebo-controlled, Phase 2 trial. The trial consisted of two parts: Part A and Part B.

Part A:
The objective of Part A was to evaluate the pharmacokinetic (PK) profile of repeated doses of CR845 in hemodialysis patients over a one-week treatment period (total of 3 doses over 1 week). A total of 24 subjects were randomized to one of the following treatment arms:

- CR845 2.5 mcg/kg (n=5)
- CR845 1.0 mcg/kg (n=7)
- CR845 0.5 mcg/kg (n=7)
- Placebo (n=5)

Part B:
The objective of Part B was to evaluate the safety and efficacy of repeated doses of CR845 compared to placebo in reducing intensity of itching over a 2-week treatment period (total of 6 doses over 2 weeks) in hemodialysis patients with uremic pruritus. A total of 65 subjects were randomized to either CR845 1 mcg/kg (n=33) or placebo (n=32). There was a 1-week run-in period where subjects evaluated their pruritus using the worst itch visual analogue scale (VAS) twice daily (morning and night; total of 14 assessments over the 1 week period).

The primary efficacy endpoint in Part B was the absolute change from baseline to the average of Week 2 worst itching (daytime and nighttime) VAS. The mean of Week 2 includes the VAS assessments on Days 12-15 (4 daytime and 4 nighttime).



Results from CLIN2005:

Table 1: Results for the Primary Efficacy Endpoint for Part B (MITT[(1)])

	CR845 1 mcg/kg (N=33)	Placebo (N=31)
Baseline		
N	33	31
Mean (SD)	68.4 (13.4)	69.5 (15.3)
Median	68	69
Range	44 – to 95	42 – to 94
Average of Week 2 (Days 12-15)		
N	32	30
Mean (SD)	35.4 (24.5)	48.3 (27.5)
Median	29	40
Range	0 – to 90	1 – to 98
Change from Baseline to Week 2 (Days 12-15)		
N	32	30
Mean (SD)	-33.1 (23.0)	-21.5 (24.8)
Median	-33	-27
Range	-87 – to 13	-66 – to 23
Treatment Difference[(2)]		
LS Mean (95% CI)	-13.0 (-23.5, -2.5)	--
P-value	0.016	--

(1) Modified Intent-To-Treat (MITT) population, defined as all randomized subjects who received at least one dose of study drug and had at least one post-baseline assessment.

(2) LS Mean and p-value based on a mixed model for repeated measures (MMRM) model with treatment, baseline VAS score, week (Weeks 1 and 2), day within week (Days 1 through 7), treatment by week interaction as fixed effects, and subject (b) (4) as the (b) (4) (b) (4) random effect.

Figure 1: Mean (±SEM) of Daily Worst Ich VAS Scores by Treatment Group and Day

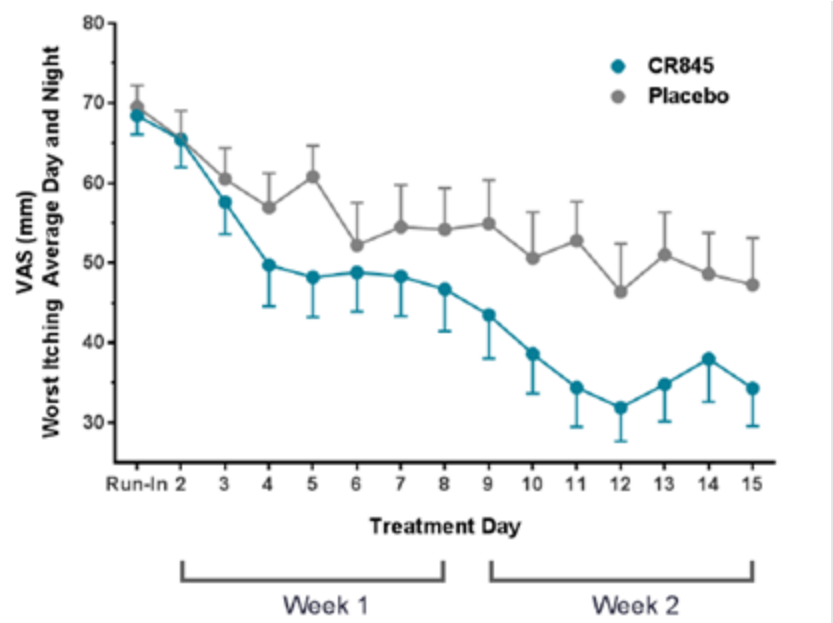
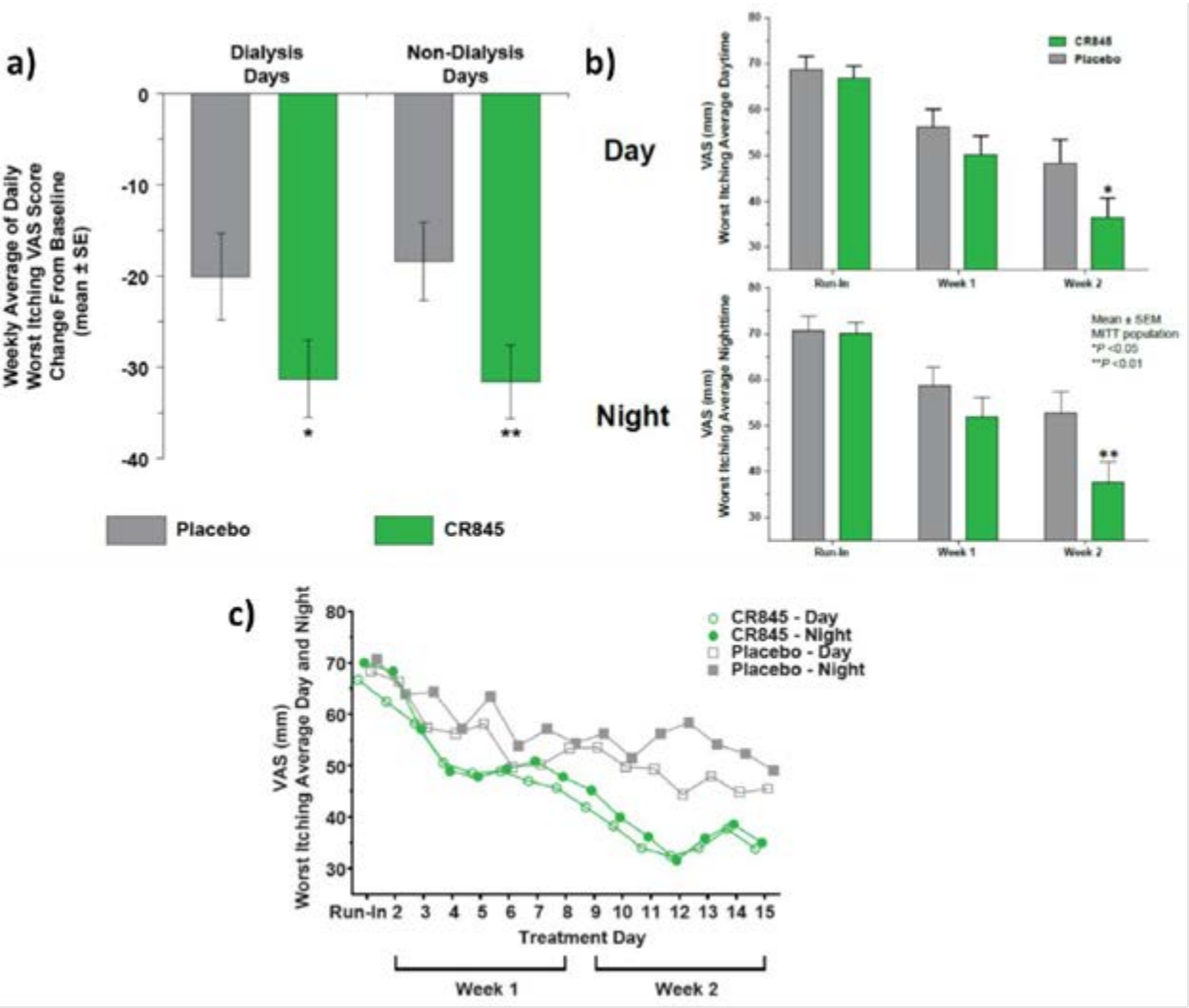


Figure 2: Worst Itch VAS Scores by Dialysis Days and Time of Day (Day v. Night)



b. The Phase 2/3 Clinical Trial: CLIN2101

Trial CLIN2101 is a two-part, multicenter, randomized, double-blind, placebo-controlled, Phase 2/3 trial to evaluate the safety and efficacy of CR845 for treatment of moderate-to-severe pruritus in hemodialysis subjects. The trial consists of the following two parts: Part A (Phase 2; dose-ranging) and Part B (Phase 3). It should be noted that the treatment periods in Part A and Part B differ, i.e., 8 weeks for Part A vs. 12 weeks for Part B. For enrollment (Part A and Part B).

Part A:

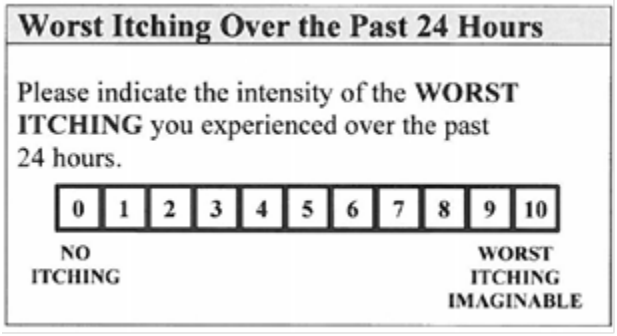
The protocol specified that enrolling and randomizing approximately 160 subjects from approximately 40 centers to one of the following treatment arms in a 1:1:1:1 ratio:

- CR845 1.5 mcg/kg (n=40)
- CR845 1.0 mcg/kg (n=40)
- CR845 0.5 mcg/kg (n=40)
- Placebo (n=40)

Subjects were administered study product as an IV bolus immediately after the end of the dialysis session during the 8-week treatment period; thus, each subject received at least 24 treatments of study product (i.e., 3 treatments per week for 8 weeks). Subjects had the following study visits: screening (Day -14 to -1), dialysis days (3 times a

week; Weeks 1 to 8), end of treatment visit (Day 57) and follow-up visit (7 days after end of treatment visit; Day 64).

The protocol-specified primary efficacy endpoint was the change from baseline to the last week of the treatment period (Week 8 for Part A, Week 12 for Part B) in the worst itch NRS. The baseline value is defined as the average daily (daytime and nighttime) worst itching NRS scores reported during the 7 days prior to randomization. The weekly mean score is defined as the sum of the daily scores reported during a specific week divided by the number of days with non-missing scores for that week.



The sponsor provided a small discussion regarding the identification of a clinically meaningful change. Specifically, the sponsor stated the following:

"Determination of the amount of change required in Worst Itching Intensity NRS scores to be clinically meaningful was estimated using various distribution-based and anchor-based methods, taking into account all of the results for the CR845-CLIN2101 study (i.e., primary, secondary and exploratory endpoints). With distribution-based approaches considered to provide a lower boundary of meaningful change (mean of distribution-based approaches = 1.31), and anchor-based approaches providing a mean minimal clinically important improvement in NRS of -2.47, a change of $\geq$ 2 points on the Worst Itching Intensity NRS is considered to represent a reasonable estimate of the true minimal clinically important improvement in NRS scores for this patient population. This change threshold, or the associated percent change (30%), is thus used in this report to define responders to CR845 treatment in HD patients with uremic pruritus."

Table 2: Weekly Mean Worst Itching Intensity NRS at Baseline and Week 8 (Population: Full Analysis)

	CR845 1.5 mcg/kg (N=44)	CR845 1 mcg/kg (N=41)	CR845 0.5 mcg/kg (N=44)	Placebo (N=45)
Baseline				
Mean (SD)	6.7 (1.4)	6.7 (1.5)	7.1 (1.4)	6.8 (1.5)
Median	6.9	6.8	7.1	6.9
Range	4.1 – 9.8	4.6 – 10.0	5.0 – 10.0	4.2 – 10.0
Week 8				
N	30	32	39	42
Mean (SD)	3.6 (2.1)	4.0 (2.1)	3.3 (2.4)	4.8 (2.7)
Median	3.4	4.3	3.1	5.6
Range	0 – 8.2	0.1 – 8.9	0 – 8.0	0.1 – 10.0
Change from Baseline to Week 8				
N	30	32	39	42
Mean (SD)	-3.3 (2.2)	-2.8 (2.2)	-3.9 (2.5)	-1.9 (2.3)
Median	-3.7	-2.8	-4.0	-1.5
Range	-8.3 – 0.7	-7.0 – 0.3	-9.0 – 1.0	-8.4 – 2.6
MMRM Analysis[(1)]				
LS Mean:				
Change from baseline to Week 8	-3.2	-2.8	-3.8	-1.9
Treatment Difference	-1.2	-0.8	-1.8	--
P-value	0.019	0.107	<0.001	--

(1) LS Mean and p-value based on a mixed model for repeated measures (MMRM) model with treatment, baseline NRS score, week, treatment by week interaction as fixed effects, (b) (4), and subject as the (b) (4) random effect.

Although the sponsor's investigation identified an absolute change of -2.47, the sponsor used percent change, which the sponsor stated is associated with a 30% change. The sponsor presented two CDF plots in the new request. Figure 3 is the CDF plot (i.e., proportion of subjects vs. treatment response [percent change in worst NRS from baseline to Week 8]) for all CR845 doses combined versus placebo. Figure 4 is the CDF plot for CR845 0.5 mcg/kg dose versus placebo. The sponsor also provided the results for the other treatment arms in table format, see Table 3.

Figure 3: CDF Plot of Percent Change in Worst Itch NRS at Week 8 for all CR845 Doses Combined vs. Placebo

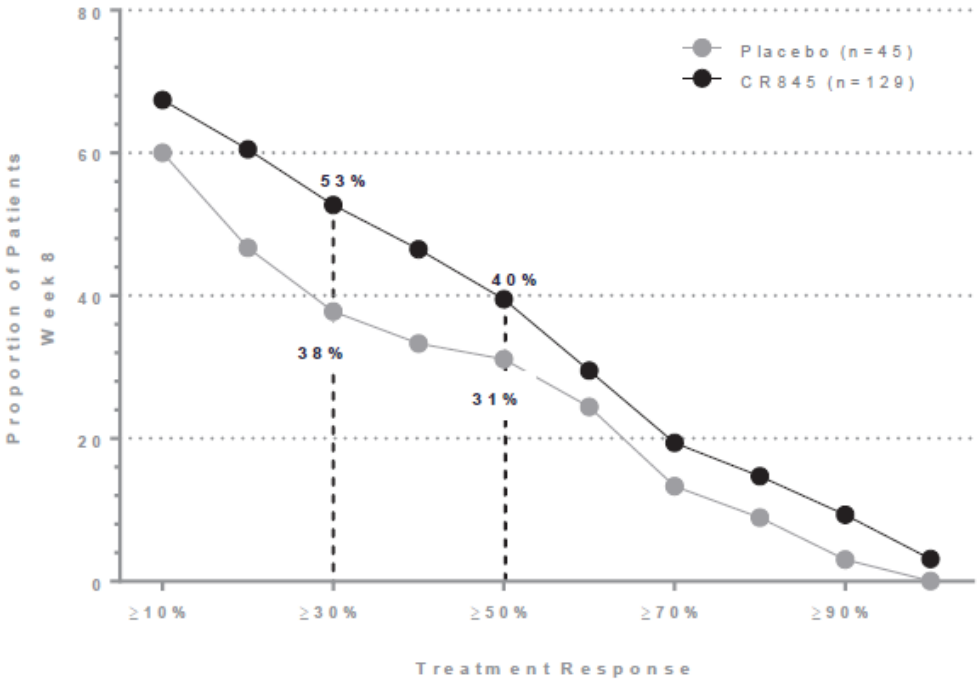


Figure 4: CDF Plot of Percent Change in Worst Itch NRS at Week 8 for CR845 0.5 mcg/kg vs. Placebo

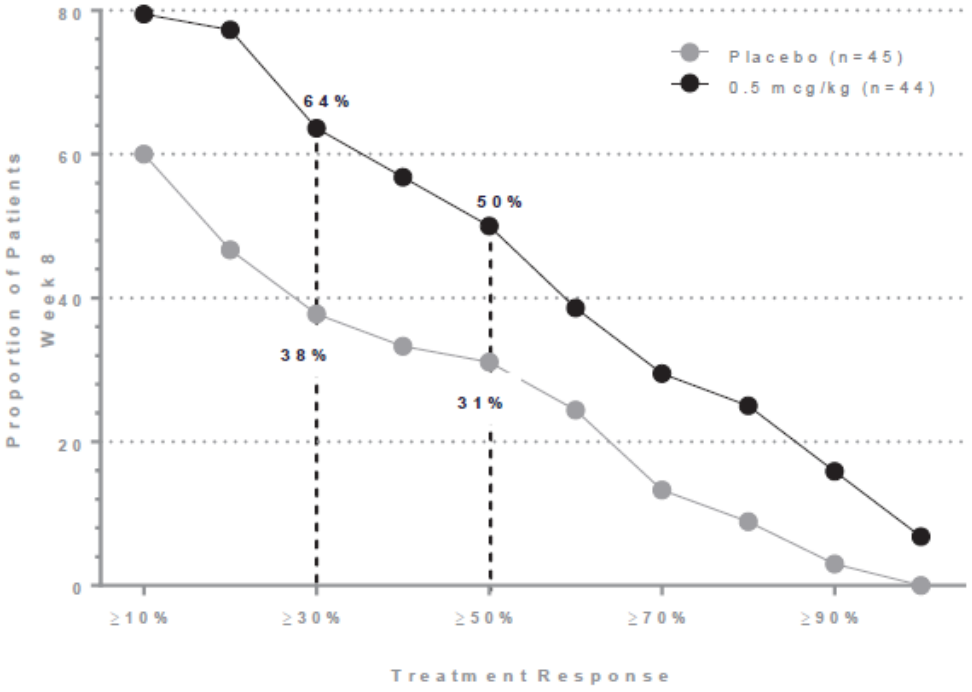


Table 3: Results for Responder Definitions (Percent Change in Worst Itch NRS) at Week 8

Responder Definition	CR845 1.5 mcg/kg (N=44)	CR845 1 mcg/kg (N=41)	CR845 0.5 mcg/kg (N=44)	Placebo (N=45)
≥10% change from baseline	26 (59%)	26 (63%)	35 (80%)	27 (60%)
≥20% change from baseline	23 (52%)	21 (51%)	34 (77%)	21 (47%)
≥30% change from baseline	22 (50%)	18 (44%)	28 (64%)	17 (38%)
≥40% change from baseline	20 (46%)	15 (37%)	25 (57%)	15 (33%)
≥50% change from baseline	17 (39%)	12 (29%)	22 (50%)	14 (31%)
≥60% change from baseline	10 (23%)	11 (27%)	17 (39%)	11 (24%)
≥70% change from baseline	6 (14%)	6 (15%)	13 (30%)	6 (13%)
≥80% change from baseline	4 (9%)	4 (10%)	11 (25%)	4 (9%)
≥90% change from baseline	3 (7%)	2 (5%)	7 (16%)	3 (7%)
≥100% change from baseline	1 (2%)	0	3 (7%)	0

(1) Subjects with missing data are imputed as non-responders.

After initial review of the (b) (4) provided results in the BTD application, the Agency requested the sponsor to submit results for responder definitions: ≥2-point, ≥3-point, and ≥4-point improvement (reduction) from baseline on the worst itch NRS at Week 8. The sponsor submitted the results for only the observed data (i.e., subjects with data at Week 8). It should be noted that the rate of missing data increased as the dose concentration increased (i.e., 7% for placebo, 11% for 0.5 mcg/kg, 22% for 1 mcg/kg, and 32% for 1.5 mcg/kg). The reasons for subject discontinuation from the trial are currently unknown as the sponsor did not provide the disposition of subjects in the BTD application.

Table 4: Results for Responder Definitions (Absolute Change in Worst Itch NRS) at Week 8

Responder Definition	CR845 1.5 mcg/kg	CR845 1 mcg/kg	CR845 0.5 mcg/kg	Placebo
Observed[(1)] (Sponsor Submitted)	N=30	N=32	N=39	N=42
≥2-point improvement	73%	53%	82%	40%
≥3-point improvement	67%	47%	64%	29%
≥4-point improvement	43%	34%	51%	24%
All Subjects[(2)]	N=44	N=41	N=44	N=45
≥2-point improvement	50%	41%	73%	38%
≥3-point improvement	45%	37%	57%	27%
≥4-point improvement	30%	27%	45%	22%

(1) Subjects with data at Week 8
(2) Subjects with missing data at Week 8 imputed as non-responders.

c. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

At the EOP2 meeting, the Division consulted the Clinical Outcomes Staff for a review of the PRO endpoints proposed by the sponsor, specifically, the outcome measure of the Worst Itching Intensity Numeric Scale (NRS) for the measurement of pruritus intensity for use as a primary endpoint in clinical trials for uremic pruritus. The review of the COA:

> *"Based on the information provided, we conclude that Cara appears to be progressing in the right direction in their patient-reported outcome (PRO) selection for their proposed primary endpoint, as an 11-point numeric rating scale (NRS) is appropriate for use to measure pruritus severity at its worst (i.e., most severe pruritus)."*

The Division has discussed the necessity for the endpoint to demonstrate a robust, clinically meaningful change with the sponsor and recommenede the sponsor submit evidence to support the propsed responder definitions and

justifications for the definition, including what constitutes clinically meaningful change. The Agency noted the recommended approach to evaluate a scale's ability to detect change, as well as generate a responder definition, is the use of anchor-based methods. Distribution-based methods and cumulative distribution function may also be useful to support a responder definition. Definitions of a responder for use in analysis of the primary endpoint should be prospectively described in the protocol and statistical analysis plan.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

The reported prevalence of uremic pruritus in adult hemodialysis patients has varied with some studies suggesting as high as 50 to 90% [3]. In one of the largest trials (the Dialysis Outcomes and Practice Patterns Study [DOPPS]), pruritus was experienced by 42% of HD patients [4].

Uremic pruritus most commonly affects the back but may also involve the arms, head, and abdomen. Generalized pruritus is also seen in significant numbers of patients. Some patients will experience pruritus for only a few minutes each day, whereas others have it nearly continuously. Symptoms tend to be worse at night, resulting in sleep disruption. Heat and stress also increases pruritus.

The pathophysiology of uremic pruritus is poorly understood. No single cause underlying uremic pruritus has been identified. Multiple factors have been associated in observational studies. The opiod hypothesis proposes that imbalance of mu and kappa opiod receptors cause prutitus. Thus, pruritus is increase by mu-receptor activation and kappa-receptor blockade and decreased by kappa-receptor activation and mu-receptor blockade.

There are currently no FDA-approved therapies indicated to treat the pruritus associated with uremic patients receiving hemodialysis. The initial therapy for all dialysis patients with uremic pruritus includes:

- Optimal dialysis
- Optimal treatment of hyperparathyroidism, hyperphosphatemia, and hypermagnesemia
- Regular use of emollients and/or topical analgesics

Off-label treatment of the pruritus of uremia include combination treatment including emollients, antihistamines, gabapentin, and anti-inflammatory medications. The use of gabapentin and prgabalin, if oral antihistamines provide no relief of symptoms after a one-week trial, may be prescribed.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[5].

None

[3] Balaskas EV, Chu M, Uldall RP, Gupta A, Oreopoulos DG. Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. *Perit Dial Int.* 1993;13 Suppl 2:S527.

[4] Pisoni RL, Wikstrom B, Elder SJ, Akizawa T, Asano Y, Keen ML, Saran R, Mendelssohn DC, Young EW, Port FK. Pruritus in hemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant.* 2006;21(12):3495.

[5] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

10. Information related to the preliminary clinical evidence:

To date, the intravenous (IV) formulation of CR845 has been evaluated in approximately 700 patients and healthy volunteers across 7 Phase 1 studies (including 2 studies conducted in Japan), 3 Phase 2 studies for the relief of moderate-to-severe, acute postoperative pain, and 2 Phase 2 studies for the relief of moderate-to-severe pruritus in hemodialysis patients. CR845 has been evaluated both as an IV bolus and a 15-minute infusion of single or repeated doses ranging from 0.5 to 40 mcg/kg. Of the patients exposed to IV CR845 to date, 213 hemodialysis patients (127 males and 86 females) have received single or repeated IV injections of CR845 doses (for up to 8 weeks) ranging from 0.5 to 6 mcg/kg across 2 Phase 1 studies and 2 Phase 2 safety and efficacy studies.

Most adverse events were mild or moderate in nature. Mild transient paresthesias (facial tingling) and/or hypoesthesias (in different anatomic locations) were experienced, mostly on the first week of dosing, as well as headache, dizziness, and somnolence, were the most frequently reported adverse events associated with CR845 administration. Psychiatric side effects (eg, dysphoria and hallucinations) commonly associated with centrally-acting kappa opioids were not reported in patients exposed to CR845. This is consistent with its lack of affinity for MORs, CR845 did not cause euphoria, respiratory depression, or reduction in oxygen saturation.

In patients on HD, a total of 34 of the 174 patients (19.5%) randomized and treated in the study experienced SAEs. Only 1 SAE was considered probably related to study drug by the Investigator for an episode of mental status changes (moderate in severity), although based on medical review by the sponsor, it was deemed that an alternate etiology of urgent/emergent hypertension may have resulted in the acute change in mental status. There were 4 patient deaths during the conduct of the study, all of which were considered not related to the study drug.

Conclusion

The Division has concluded that CR845 intravenous therapy for the treatment of moderate to severe pruritus associated with hemodialysis in subject with end-stage renal failure, there is suffcient data to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints . In the opinion of this reviewer, the Breakthough Therapy Designation should be granted to Cara for CR845.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

Sufficient clinical evidence exists, from a clinically substantial endpoint of Worst Itch NRS, that CR845 is an improvement over existing therapies for patients with moderate to severe pruritus who are on hemodialysis.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

Once the BTDR is granted, the Division will work with the sponsor to further the development plan for CR845, including granting a second End-of-Phase 2 meeting to discuss product development.

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAYLA J GARVIN
06/13/2017

JILL A LINDSTROM
06/13/2017